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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/755,747	01/05/2001	Anthony J. Brookes	78104.017	3891

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EXAMINER
FREDMAN, JEFFREY NORMAN

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 04/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/755,747	BROOKES, ANTHONY J.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5, 7-18, 20-31, 33-44, 46-70* is/are pending in the application.

4a) Of the above claim(s) *53-66* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-18,20-31,33-44,46-52 and 67-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 19, 2003 has been entered.

Claim Objections

2. The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claims 53-56 have been renumbered 67-70.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1-5, 8, 10-18, 21, 23-31, 34, 36-44, 47, 49-52 and 67-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Drobyshev et al (Gene (1997) 188:45-52) in view of Wittwer (U.S. Patent 6,174,670).

Drobyshev teaches a method of detecting DNA variation by monitoring the formation or dissociation of a of a complex (abstract) consisting of:

(a) a single strand of a DNA sequence (here the 10 mer oligonucleotide attached to the solid support which is a solid surface as broadly interpreted (page 46, column 2, subheading "oligonucleotide microchip"),

(b) an oligonucleotide specific for the single stranded DNA sequence specific for one allele of the variation and capable of hybridizing to the single strand (a) to form a duplex (here the RNA transcript (page 46, figure 1 and page 47, subheading "RNA samples")

(c) a marker detection of the duplex structure of (a) plus (b) which forms a complex with the said duplex (here the fluorescent labels fluorescein and rhodamine (page 51, column 1),

which method comprises:

(1) continually measuring an output signal indicative of the duplex formed from the strand (a) and probe (b) (see page 49, figure 2) and

(2) recording the conditions at which a change in reaction output signal occurs which is attributable to formation or dissociation of the complex and is thereby correlated with the strength with which the probe (b) has hybridized to the single strand (a) (see page 49, figure 2).

Drobyshev further teaches formation of two or more complexes, each with a probe specific for a different allele of the variaition, and observing their respective denaturing or annealing conditions to distinguish alleles of the variation (page 49, figure 2).

Drobyshev does not teach the use of a marker which is duplex specific in the analysis.

Wittwer et al teaches a method of detecting DNA variation by monitoring the formation or dissociation of a complex (abstract) consisting of:

(a) a single strand of a DNA sequence (here denatured genomic DNA (column 9, line 21) and/or denatured amplified PCR products, including an 81 basepair cystic fibrosis gene product (column 40, lines 58-67)) as well as many longer PCR products such as the 536 base pair b-globin sequence (column 47, line 24),

(b) an oligonucleotide specific for the single stranded DNA sequence (here either the primers used in PCR (column 41, lines 1-20) or pairs of fluorescently labeled oligonucleotide probes (column 9, lines 27-37)),

(c) a marker specific for the duplex structure of (a) plus (b) which forms a complex with the said duplex and reacts uniquely when interacting within the duplex (here either SYBR green, (see column 40, line 65) or the fluorescence resonance energy transfer pair of labels, which differentially fluoresce when in duplex or single stranded states (column 9, lines 27-37)),

which method comprises:

(1) continually measuring an output signal indicative of interaction of the marker with duplex formed from the strand (a) and probe (b) (see column 9, lines 50-55 or column 41, lines 14-17 and figure 43) and

(2) recording the conditions at which a change in reaction output signal occurs which is attributable to formation or dissociation of the complex and is thereby correlated with the strength with which the probe (b) has hybridized to the single strand (a) (see page column 9, lines 55-59 or column 41, lines 14-17 and figure 43).

Column 14 details a similar assay for differentiating the Factor V Leiden mutation. Column 46 teaches the use of two or more complexes of the kind defined, each with a probe specific for a different allele of the mutation which multiple detection probes are distinguished by the different melting peaks (see column 46, lines 49-61). Wittwer further teaches measurement of the annealing based upon the first or second derivatives of the fluorescent melting curves (column 12 and columns 23-26) and expressly discusses measurement of the second order rate constant (see column 12).

Wittwer expressly teaches with regard to new claims 67-70 that "The melting curves are easiest to visualize by plotting the negative derivative of fluorescence with respect to temperature vs temperature (-dF/dT vs T) (column 45, lines 10-14)". Thus, with regard to the negative derivative of the fluorescent measurement, Wittwer is teaching determining the presence of a peak. Wittwer is clearly showing the presence of peaks in figure 46 B, where the homozygous and heterozygous (termed match and mismatch in the claim) are separately identified using the negative derivative data analysis method.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the markers of Wittwer in the mutation detection method of Drobyshev since Wittwer states "SYBR™ Green I is a preferred double strand specific dye for fluorescence monitoring of PCR, primarily because of superior sensitivity, arising from greater discrimination between double stranded and single stranded nucleic acid. SYBR™ Green I can be used in any amplification and is inexpensive. In addition, product specificity can be obtained by analysis of melting curves, as will be described momentarily (column 23, lines 9-16)". Thus, an ordinary practitioner would have been motivated to use SYBR™ Green I in the melting curve analytical method of Drobyshev since Wittwer teaches that this intercalator is superior in sensitivity, is useful in the particular assay employed by Drobyshev and is inexpensive.

3. Claims 1-5, 7, 8, 10-18, 20, 21, 23-31, 33, 34, 36-44, 46, 47, 49-52 and 67-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Drobyshev et al (Gene (1997) 188:45-52) in view of Wittwer (U.S. Patent 6,174,670) and further in view of Heller et al (U.S. Patent 6,048,690).

Drobyshev in view of Wittwer teach the limitations of claims 1-5, 8, 10-18, 21, 23-31, 34, 36-44, 47, 49-52 and 67-70 as discussed above. Drobyshev in view of Wittwer do not teach immobilization of the oligonucleotide using biotin-streptavidin.

Heller teaches immobilization of oligonucleotides to arrays using biotin-streptavidin for nucleic acid detection assays (column 16, lines 62-67).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the method of Heller in the detection method of Drobyshev in view of Wittwer since Heller states "In this example, the first probe (a capture/quencher probe sequence) has two terminal functional groups, a 5'-terminal biotin group which allows the probe to be immobilized to the surface (permeation layer) of a microlocation test site on an active DNA chip or other hybridization device." (column 16, lines 62-67). An ordinary practitioner would have been motivated to use the biotin capture method in order to permit immobilization of probes to desired microlocations of DNA chips for the analytical method. Also, an ordinary practitioner would be motivated to select a known equivalent of the method of Drobyshev for attachment of the nucleic acids to the array as Drobyshev notes a variety of attachment mechanisms (page 45, column 2).

4. Claims 1-6, 8-19, 21-32, 34-45, 47-52, 67-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Drobyshev et al (Gene (1997) 188:45-52) in view of Wittwer (U.S. Patent 6,174,670) and further in view of Konrad et al (U.S. Patent 5,789,167).

Drobyshev in view of Wittwer teach the limitations of claims 1-5, 8, 10-18, 21, 23-31, 34, 36-44, 47, 49-52, 67-70 as discussed above. Drobyshev in view of Wittwer do not teach the use of Hepes buffer in hybridization.

Konrad teaches that " The conditions for hybridization of oligonucleotide sequences are well known. Generally, the hybridization step is either performed in a buffered aqueous salt solution at high temperature or in the presence of formamide at lower temperature. The aqueous, high temperature procedure is typically carried out

in a Tris buffer, such as 0.3M NaCl, 20 mM Tris -HCl, pH 6.8, at 67.degree. C. Other buffering systems such as hepes or glycine-NaOH and potassium phosphate buffers can be used. (column 14, lines 59-67)".

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the Hepes buffer of Konrad in the detection method of Drobyshev in view of Wittwer since Konrad expressly teaches that Hepes buffer is an equivalent buffer for use in hybridization reactions.

Response to Arguments

5. Applicant's arguments filed February 19, 2003 have been fully considered but they are not persuasive.

Applicant requested that the Patent Office amplify the reasons why the declaration and the arguments regarding why polyacrylamide is not solid surface were not found persuasive. There are two separate lines of reasoning which support the reasoning of the rejection.

First, as noted previously, a Polyacrylamide gel can be considered a solid surface by the skilled artisan is evidenced by Patent Publication 2002/0109841, which states "on a two dimensional surface such as a glass microscope slide, polyacrylamide gel, silicon microarray, or other solid surfaces . (see column 4, lines 2-4)". Also, Drobyshev himself is at pains to say that the reaction "looks more like a liquid phase than a solid-phase interaction (see page 48, column 1)", which shows that Drobyshev understands the interaction to be solid-phase. Drobyshev states that the polyacrylamide gel "provides a stable three dimensional support" (see page 48, column

1) which must therefore be solid. Further, the specification does not, in any way, define the term "solid surface". Therefore, the ordinary meaning of the term "solid" is that the object is neither a liquid nor a gas. Applicant cites to dictionary definitions of the word "surface", but these definitions obscure more than they illuminate. For example, in the definitions cited, a surface may be "a layer of something". The polyacrylamide gel is clearly a layer within the meaning of the term cited. Another definition calls a surface "A material layer constituting such a boundary". Again, the polyacrylamide gel is such a layer. Polyacrylamide is clearly neither a liquid nor a gas and therefore meets the ordinary meaning of the term "solid". This argument therefore relies upon the understanding of either the skilled artisan or the ordinary meaning to indicate that the polyacrylamide gel is a "solid" surface. The declaration is addressed by the understanding of the ordinary artisan as discussed above. The citation of the Pgpub document simply shows that a polyacrylamide gel is a "material layer" (defined by Applicant's dictionaries as a surface" equivalent to a microarray.

Second, if the first argument were not persuasive, the claim states "bound to a solid surface". MPEP 2111 commands that "During patent examination, the pending claims must be "given the broadest reasonable interpretation consistent with the specification." In this case, the broadest reasonable interpretation, assuming for argument's sake that the polyacrylamide gel is not a solid surface, is to treat bound as either directly or indirectly bound and to note that the oligonucleotide of Drobyshev is bound to the polyacrylamide which is itself bound to a glass surface (see page 49, figure 2). Consequently, the oligonucleotide is bound, indirectly, to glass, which is

unarguably a solid surface. Therefore, the broadest reasonable interpretation of the claim is that the oligonucleotide of Drobyshev, bound via polyacrylamide to glass, is clearly bound to a solid surface of glass, even if the polyacrylamide itself is not deemed a solid surface.

Applicant then repeats the arguments that the references do not teach the use of a solid surface. As noted above, this is incorrect both when the term "solid surface" is properly interpreted and when the claim is given it's broadest reasonable interpretation.

6. Applicant argues that the three dimensional arrangement of Drobyshev is not equivalent to a single layer of oligonucleotides bound to a solid surface. This is not a limitation of the claims. There is no basis in the claims and no limitation was found in the claims, that the oligonucleotides must be formed in a single layer. This feature is not recited in the claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). In fact, the limitation was not found in the specification either.

The citation of other art does not disturb the obviousness argument. The modification necessary to render the claims obvious is not the three dimensional versus two dimensional nature of the array. The modification to Drobyshev is the use of Sybr green dye for detection. The rejection provides strong motivation to detect using Sybr Green.

Applicant then repeats the argument that there would not be motivation to use SYBR green in the methods of Drobyshev. This argument is not found persuasive

because Drobyshev expressly monitors hybridization by measurement of melting curves, just as Wittwer does, and the advantages disclosed by Wittwer in the use of SYBR green would be directly applicable and expected to apply to the Drobyshev method. Applicant attempts to limit Wittwer by citing another embodiment taught by Wittwer. As MPEP 2123 notes " Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi,169 USPQ 423." Here, the disclosed example and embodiment of the FRET assay does not teach away from the use of SYBR green. As a separate point, since hybridization of either DNA or RNA operates by the same mechanism and since SYBR green interacts with both DNA and RNA (see Spiess et al (Biotechniques (1999) 26:46-48 attached for evidence of interaction of SYBR green with RNA) either type of molecule would have been prima facie obvious.

Applicant then argues the rejection with regard to Heller. Applicant argues Heller alone, without combining the teachings of Drobyshev and Wittwer. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Heller is relied upon solely to teach that biotin-streptavidin binding to surfaces is a desirable and well known method for immobilization of nucleic acids onto solid surfaces. Applicant has not shown that the high temperature was, in any way,

unexpected. With regard to the argument of unexpected results, MPEP 716.01(c) makes clear that

> "The arguments of counsel cannot take the place of evidence in the record. In re Schulze , 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results."

In the current case, no evidence of unexpected results is demonstrated.

Applicant similiarly argues the rejection further in view of Konrad without combining the references. Recognition of equivalents is a well known basis for substitution. As MPEP 2144.06 notes "In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art." Here, the prior art reference of Konrad, cited for the rejection, expressly states that Tris and Hepes are known equivalents. MPEP 2144.06 continues to state "An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982)." As above, Applicant has not provided any evidence of unexpected results.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers

for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jeffrey Fredman
Primary Examiner
Art Unit 1637

March 28, 2003